UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,515	03/19/2004	Masayoshi Yamaguchi	671302-2006	7637

20999 7590 06/19/2007
FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
06/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,515	YAMAGUCHI, MASAYOSHI	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-30,33,35-46,48 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-30,33,35-46,48 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/19/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/29/07; 4/4//07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's response to the restriction requirement was received on 9/29/2005. Claims 1-40 were pending in the instant application. Applicants elected the subject matter of Group III, claims 25-40, drawn to a drawn to an animal model having bone pathology, wherein the animal model over expresses regucalcin and shows bone pathology, a screening method of preventive and therapeutic agents, and a therapeutic agent. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

Applicants' amendment to the claims filed April 4, 2007 has been received and entered. Claims 25-30, 33, 35-36, 41-46, 48, 50 have been amended, while claims 1-24, 31-32, 34, 40, 47 and 49 have been canceled. Claims 25-30, 33, 35-39, 41-46, 48, 50-53 are pending.

Claims 25-30, 33, 35-39, 41-46, 48, 50-53 are currently under consideration. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Withdrawn-Specification

The objection to the disclosure is withdrawn in view of applicant's submission of substitute specification.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-30, 33, 35-39, 41-46, 48, 50-53 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat comprising in its genome a transgene comprising the rat regucalcin cDNA, wherein the said transgenic rat overexpresses regucalcin, and shows a decrease in bone density, bone strength and bone thickness, a method of using said transgenic rat in a screening method for preventative and therapeutic agents, does not reasonably provide enablement for any mouse that over expresses regucalcin or any transgenic rat showing any other bone pathology, a method of using said animal in a screening method for preventative and therapeutic agents for any bone disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary

skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

These claims are broad in scope, encompassing a transgenic rat or mouse model subsequently limiting to rat that overexpresses regucalcin and shows any bone pathology, wherein the changes in bone morphology are detected by measuring any changes in vulnerability of bone tissue, change of bone morphology, delay in bone growth. Further, the claims encompass using any of these animals in a screening method for preventative and therapeutic agents. The aspects considered broad are: transgenic rat and mouse model embracing both mouse and rat showing any bone pathology using any construct to over express regucalcin (emphasis added) and method of using said transgenic rat or mouse for screening therapeutics against bone disease associated with vulnerability of bone tissue, bone resorption or delay in bone growth. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

The specification teaches a transgenic nonhuman animal model having bone pathology wherein the animal model is a non-human animal that overexpresses regucalcin and shows bone pathology. See paragraph 18 of the specification. The specification further asserts a screening method of preventive and therapeutic agents for bone diseases wherein a test substance is administered to a animal model having bone pathology. See paragraph 19 of the specification. The specification has contemplated morphological measurement estimation of bone in the transgenic nonhuman animal is one or more of any of bone density, bone strength, bone thickness of diaphyseal cortex or length of surrounding of cortex. It is noted that biochemical measurement estimation of bone component is one or more of amount of calcium, alkaline phosphatase activity or amount of DNA in bone tissues. The guidance provided by the specification correlated only to a transgenic homozygous rat that overexpresses regucalcin and shows delay in bone growth and bone resorption. It is unpredictable if a

transgenic mouse would express regucalcin at adequate level to show any pathology disclosed in the instant application. In addition, certain claims (claims 25, 27-30, 33, 35-38, 41-52) embrace any bone pathology that is measured either morphologically or biochemically. The specification while provides guidance and exemplified method to study bone density, bone strength, thickness of cortial bone of diaphysis and length of surrounding outer membrane of cortex in diaphysis (see example 4, page 44), but fails to provide guidance to study any other bone pathology associated with genus of bone disease in the transgenic mouse or rat having "any vulnerability of bone tissue, bone resorption or delay in bone growth." It is unclear how a decrease in "any vulnerability of bone tissue" is pathological. An artisan would have to perform undue experimentation to make and use of invention.

As a first issue, amended claims 25, 27-30, 33, 35-39, 41,43-46, 48, 51-53 embrace a transgenic homozygous rat or mouse model having bone pathology wherein said model is a rat or mouse that overexpresses regucalcin having bone pathology comprising vulnerability of bone tissue, bone resorption or delay in bone growth. As amended it is unclear if claims requires mouse or rat homozygous for regucalcin or any other gene. The specification contemplates a transgenic non-human animal wherein the regucalcin gene is introduced resulting in over expression of regucalcin. The specification has asserted that such a nonhuman could be created by injecting an expression vector (pCXN2) comprising a chicken beta-actin promoter operably linked to regucalcin cDNA. The specification has provided a working example correlating only to a method of generating homozygous transgenic rat containing a construct comprising a chicken beta-actin promoter operably linked to regucalcin gene that overexpresses regucalcin (emphasis added). It is noted that resulting transgenic rat and shows delay in bone growth and bone resorption. It is emphasized that neither specification nor art or record explicitly teaches whether any other transgenic other then one exemplified in the specification would result same phenotype as recited in instant claims. While the art of transgenics is such that one of skill in the art would be able to produce a transgenic rat comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For

instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic rat are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. These issues become even more complicated when working with more than one transgene, especially when the products of one transgene regulate the expression of the other. The complex problems associated with transgenesis are illustrated by Houdebine et al., who states "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes; Art of record). Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other animals (pg. 310, col. 1, para 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, para 3). As Murray states, "the observation that the oMT1a-oGH transgene that is regulated in mice is uncontrollable in both sheep and pigs suggests that transgene constructs still need to be tested in the species of interest" (Murray (1999) Theriogenology 51:149-159; pg. 150, para 4; Art of record). These observations are specifically supported by Hammer et al. (Journal of animal Science, 1986, 63, 269-278) who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al (Mol Endocrinol. 1988; 2(3): 277-83) report a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin

fusion gene (p. 277, summarized in abstract). In addition, Mullins et al (Nature, 1990, 344; 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin trasngene. Hammer et al (Cell, 1990, 63: 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both the investigators were preceded by the failure to develop human disease like symptoms in transgenic mice (Mullins, 1989, EMBO, 8: 4065-4072; Taurog, 1988, J. Immunology, 141: 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. This observation is further supported by Mullins (Journal of Clinical Investigation, 1996, 97, 1557-1560, art of record) who report on transgenesis in the rat and larger mammals. Mullins et al. state "a given construct may react very differently from one species to another" (see Summary section). Thus, without evidence to the contrary, transgene expression in mouse and rat is not predictable and varies according to the particular host species. Given species differences in the expression of various transgenes, one of skill in the art would have been required to undergo undue experimentation to determine which promoters and specific transgene constructs would produce the desired phenotype in mouse. In the instant case, the specific elements used in the construction of the DNA plasmid for use in generating the transgenic rat were not discovered by Applicant, rather they were derived from the art based on reports of their function in rat. Absent of evidence to the contrary, it is not clear that these elements would be functional in mouse in the same manner as they have been demonstrated in the transgenic rat.

Claims 36-39 and 50-53 are directed to a screening method of preventive and therapeutic agent for bone disease by administering test agent to the transgenic rat or mouse of the invention showing bone pathology associated with vulnerability of bone tissue, bone resorption or delay in bone growth. The disclosure provided guidance in terms of expression level of regucalcin and pathology associated with it, but it does not provide any guidance in terms of its functional involvement in specific bone disease or osteoporosis nor does it disclose a relationship to a condition associated with any bone

disease that could be treated by any agent identified by the instant methods. Therefore, an artisan would not know all the functions of regucalcin and would not know of any known relationship to all the disease or conditions. Furthermore, for an artisan to use or make the instant method for its intended use, an artisan would have to determine the function of regucalcin and if there are any disease or specific conditions associated with over expression of regucalcin. Therefore, given the fact that an artisan would not know how to make or use the instant method for screening an agent for any bone disease as broadly claimed. It is emphasized that the specification does not provide any specific guidance for the use of a method for screening agents that treats bone diseases arising from all different types of pathology and etiology. The specification teaches that agents identified through the screening method of the invention are potential therapeutics for use in a number of conditions including osteoporosis, preclinical study, clarification of the bone pathology mechanism or the development of a new drug (see specification paragraph 158). Chenug et al (Bone. 2006; 39(3): 470-6) describe osteoporosis pseudoglioma syndrome (OPPG), which is an autosomal recessive disorder due to mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene. It is noted that patients suffering from OPPG show blindness, low bone mineral density (BMD) and multiple fractures in their childhood. In addition, genotyping by DNA sequencing demonstrated 2 new mutations in exon 7 of the LRP5 gene. Thus, it is apparent that instant transgenic rat model would not truly represent the etiology and pathology associated with bone disease associated with OPPG. Therefore, given the complex genetic and other contributing factors for a bone disease the multiple pathologies that arise in a given bone disease cannot be representative in current transgenic rat or mouse models which may be most productively used to examine the bone density and growth rather than as comprehensive models of complex bone diseases or osteoporosis as broadly recited.

It is noted that specification does not provide any specific teaching regarding how individual symptoms of different bone disease are related specifically to any condition or type of agents, amount needed, dosage schedule and delivery route that would be used to identify the agent. An artisan would have to perform undue

experimentation to first establish a link between the transgenic rat or mouse with a specific condition and then test various parameters using different type of agents, dosage and delivery route in order to reduce symptoms seen the transgenic animal of the invention. It is emphasized that bone pathology in disease or condition can be caused by a variety of mechanism that may or may not have any involvement of regucalcin gene. Given that the specification and art do not disclose nexus between any known disease and over expression of regucalcin, an artisan would not know if the instant transgenic mouse or rat represent a model for bone pathology associated with bone disease of different pathology and etiology It is emphasized that specification only enables to a transgenic rat model that shows phenotype of decrease in bone density, bone strength and bone thickness. An artisan would have to do further experimentation to determine if the symptoms associated with the transgenic rat are representative of any specific disease or condition or representative of all bone diseases. In addition, an artisan would not know if the any particular agent identified using instant transgenic mouse would be able to treat a disease symptom similar to those observed in the transgenic rat. In view of foregoing discussion, it is apparent that any difference of symptom seen in the instant transgenic rat cannot be generally associated with any complex bone disease arising from different mechanism. Therefore, an artisan would not know if the compounds identified by measuring morphological or biochemical parameter in the transgenic rat of the invention would be effective for its intended use in the treatment or prevention of any bone disease other then those specifically recited in claims 25-26 of the instant application.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with full scope of the claims. The specification and prior art do not teach a transgenic mice over expressing regucalcin and showing bone pathology arising from any disease or screening method for preventing or treating any bone disease. An artisan of skill would have perform undue experimentation to practice

the method as claimed because the art of transgenics was evolving and unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant's arguments filed 4/04/2007 have been fully considered but they are not fully persuasive. Applicant argues that the rejection fails to provide a fact based analysis using the "Wands" factors that supports the proposition the claimed invention require undue experimentation (see page 8 of the arguments). Applicant also assert that claims 25 and 41 have been amended to clarify that the transgenic rat or mouse is homozygous, and that the bone pathology comprises vulnerability of bone tissue, bone resorption, or delay in bone growth. Applicants also argues that claims 36 and 50 are amended to clarify that the cited bone diseases are associated with vulnerability of bone tissue, bone resorption, or delay in bone growth. Accordingly, one skilled in the art is enabled to practice the invention as disclosed in the instant claims without undue experimentation. Applicants also argues that instant specification provide working examples and guidance sufficiently enable an artisan to practice the instant invention. Applicants also assert that mice and rats are very similar, and that 30% of the rat genome aligns only with the mouse genome (Gibbs et al. Nature 428: 493-521, 2004). Mice are commonly used as transgenic models due to the relative ease in manipulating their genome (Malakoff. Science 288: 248-253, 2000), and are especially utilized in the study of bone diseases and pathologies such as osteoporosis (Xu et al. Nat Genet 20: 78-82, 1998; Ferrari et al Curr Opin Lipidol 16: 207-213, 2005), osteopetrosis (Saftig et al. Proc Natl Acad Sci USA 95: 13453-13458, 1998), and osteomalacia (Leheste et al. FASEB J 17:247-249, 2003). Applicants also ague that it is known that bone pathologies in mice and rats are similar; as analogous protocols have been applied to both rats and mice to study such disease as osteoporosis (David et al. J Bone Mineral Res 18:1622-1631, 2003; Aguirre et al. J Bone Mineral Res 21 : 605-615, 2006). In addition, applicants also argue that specification indicates that regucalcin is expressed

in mice, while the state of the art indicates that the presence of regucalcin in mouse marrow cultures stimulates osteoclast-like cells formation (Yamaguchi et al. J Cell Biochem 94: 794-803, 2005). Applicants assert that given the prior and state of art, a skilled artisan would be enabled to generate transgenic mice as disclosed in the instant claims without undue experimentation, especially considering the ease at which transgenic mice can be formed and the effects of regucalcin on mice cells.

These arguments are fully considered but are not found to be fully persuasive. In part this is due to the breadth of applicant's claims that embraces a transgenic homozygous rat or mouse model having bone pathology comprising vulnerability of bone pathology, bone resorption or delay in bone growth in mouse or rat model that over expresses regucalcin showing said pathology. Applicant's working examples are limited to the disclosure of a transgenic rat comprising in its genome a transgene comprising the rat regucalcin cDNA, wherein the said transgenic rat overexpresses regucalcin, and shows a decrease in bone density, bone strength and bone thickness. It is emphasized as amended claims still read on any transgenic homozygous rat or mouse that is homozygous for any gene and over expresses regucalcin. For instance, homozygous transgenic mouse or rat for a transgene that over expresses regucalcin are broadly embraced by the claims. In view of the longstanding teachings in the art specification does not provide guidance for the full breadth of the claims. Claims do not link the homozygous nature to regucalcin transgene. As previously stated: The state of the art of transgenics was not a predictable art with respect to transgene behavior and the resulting phenotype at the time of filing of this application. While the art of transgenics is such that one of skill in the art would be able to produce a transgenic rat or mice comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic rat are directly dependent on the specific transgene construct including individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all

important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. These issues become even more complicated when working with more than one transgene, especially when the products of one transgene regulate the expression of the other. In the instant case, claims as recited read on any transgenic homozygous rat or mouse that over expresses regucalcin. The specification has provided guidance with respect to a transgenic rat comprising in its genome a transgene comprising the rat regucalcin cDNA, wherein the said transgenic rat overexpresses regucalcin, and shows bone pathology consistent with phenotype set forth in claim 25. It is emphasized that resulting phenotype of transgenic mouse or rat homozygous for any transgene was considered unpredictable. This complex problems associated with transgenesis are illustrated by Houdebine et al., who states "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes). Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other animals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, pgph 3). In response to applicants' argument that prior art indicated bone pathologies are similar in mouse and rat and art indicated presence of regucalcin in mouse marrow stimulating osteoclast cell formation. In response to applicant's, it is noted that the features upon which applicant relies (i.e., osteoclast formation in marrow of mice cited in Yamaguchi et al J Cell Biochem (2005) 94: 794-803) were not known at the time of filing of this application. In fact, several years after filing of this application, Yamaguchi et al showed regucalcin directly stimulates osteoclast-like cell formation in mouse marrow culture in vitro, and that the protein stimulates bone resorption in rat femoral tissues in vitro. It is emphasized that neither instant specification nor prior art provided adequate guidance in this regard prior to instant invention. Given, the lack of guidance provided

by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

In response to applicants' argument that mice and rats are very similar and asserts that exemplifying transgenes that successfully expressed in rats but did not express in mice cited by examiner uses a blood pressure gene that is much different than gene involved in the instant case that results in different pathology. Examiner would agree that mice and rats are similar and analogous protocols have been applied to both rats and mice to study such bone disease. However, in the instant case, claim are drawn to an rat or mice model having bone pathology comprising vulnerability of bone tissue, bone resorption subsequently limiting to a screening method of preventive and therapeutic agent for said bone pathology which is osteoporosis. Examiner had cited references to demonstrate that a given construct react very differently from one species to another (supra, Mullins et al). The references of Murray et al, Ebert et al and Hammer et al is included to demonstrate that transgenic animal of a given phenotype are sensitive to numerous factor at the time of filing of this application. Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype is not predictable. Contrary to applicants argument Examiner had indicated unpredictability in transposing the effects of a transgene across animals that included pigs, sheep and mice but also included references showing that expression the same transgenes that successfully caused the desired symptoms in transgenic rats failed to develop human disease like symptoms in transgenic mice (see (Mullins et al and Taurog, supra). In the instant case, the issue is not whether the cited art used same transgene; rather issue is whether disclosed elements would be functional in mice in the same manner, as they have been demonstrated in the transgenic rat. Examiner has cited reference to indicate unpredictability in transposing the effects of a transgene in mice or rat. This is particularly important since random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype. While the intent is not

to say transgenic mice or rat of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled commensurate with full scope. Given such differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic rat or mice other then one exemplified in the specification (emphasis added) with any specific phenotype, it would have required undue experimentation to establish the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991)*. It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*.

It is noted that claims still read on a method for screening preventive or therapeutic agent for bone disease associated vulnerability of bone tissue, bone resorption, or delay in bone growth. However, neither specification nor prior art provide any nexus between any known disease or osteoporosis and over expression of regucalcin, an artisan would not know if the instant transgenic mouse or rat represent a model for bone pathology associated with bone disease of different pathology as set forth in the claims. It is emphasized that specification only enables to a transgenic rat model that shows phenotype of decrease in bone density, bone strength and bone thickness as stated in previous office action.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632